Claims 1, 8, 10, and 11 are amended for clarity, and to more particularly point out and distinctly claim the invention. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 8, 10, and 11 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: page 27, line 23 to page 29, line 5. Accordingly, no new matter is added by these amendments.

Claims 17-24 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

New claims 25-27 are added. Support for new claims 25 and 26 is found throughout the specification, and in particular on page 24, lines 10-22. Support for new claim 27 is found throughout the specification, and in particular on page 27, line 23 to page 29, line 5.

For the Examiner's convenience, a copy of the pending claims as amended is provided in an Appendix attached hereto.

Telephonic interview

Applicants' representative thanks the Examiner for the courtesy of the telephonic interview which took place on October 4, 2000, and which was attended by Carol L. Francis, Paula A. Borden, Nelson Freimer, and the Examiner. The enablement rejection and the written description rejection of the claims under 35 U.S.C. §112, first paragraph, were discussed.

Rejection under 35 U.S.C. §112, first paragraph ("enablement")

Claims 1-12 and 17-24 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification allegedly does not enable one skilled in the art to make and use the invention commensurate in scope with these claims.

The instant invention

Before the rejections are addressed, a few comments about the invention are believed to be in order. Applicants have described in great detail:

(1) Identification of a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.

(2) Identification of polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29.

(3) How additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

(4) How individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

Method of detecting an increased susceptibility to BP (Claims 17-24)

The Office Action stated that the specification is enabling for a method of detecting an increased susceptibility for bipolar mood disorder (BP) by performing a pedigree analysis for the individual's family and analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of the markers listed. Applicants note that, while the additional method steps of analyzing DNA samples from family member may be performed to analyze susceptibility of family members to develop BP, the method does not require analysis of family members. Instead, the method can be performed on an individual to analyze susceptibility of the individual to develop BP. As noted above, this has been described in detail in the specification. Applicants delineated a small interval on chromosome 18p as containing polymorphisms associated with BP. Subsequently, an unscreened population was analyzed for the presence of the affected haplotype. Specification, page 29, lines 23-29. Thus, by analyzing a DNA sample from test individuals (members of the unscreened population) for the presence of polymorphisms on disease chromosomes,

an assessment of susceptibility to develop BP in these individuals can be made. Accordingly, the specification is enabling for the method as claimed.

Nevertheless, and solely in the interest of expediting prosecution, claims 17-24 are canceled, and claim 1 is amended to recite a method of detecting an increased susceptibility to BP, comprising analyzing a sample of DNA from a test individual for the presence of a DNA polymorphism on the short arm of chromosome 18 between SAVA5 and ga203, wherein the presence in the test individual of a polymorphism which is present on a disease chromosome indicates that the test individual has an increased susceptibility to develop BP.

Method of detecting a polymorphism associated with BP (Claims 1-12)

The Office Action stated that the specification does not enable a person skilled in the art to detect a bipolar mood disorder locus or polymorphism within the recited region without undue experimentation. Applicants respectfully traverse.

The cited art does not support a conclusion of non-enablement of the instant claims.

The Office Action cited various publications in support of the contention that the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar (BP) susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field. The cited art are Stine et al. ((1995) *Am. J. Hum. Genet.* 57:1384-1394); McInnes et al. ((1996) *Proc. Natl. Acad. Sci.* 93:13060-13065;); Esterling et al. ((1997) *Molec. Psychiatry* 2:501-504); Ewald et al. ((1997) *Psychiatric Genetics* 7:1-12); Gershon et al. ((1998) *Neuropsychopharmacology* 18:233-242); and Nöthen et al. ((1999) *Molec. Psychiatry* 4:76-84").

The present invention is based on studies that differed from previous studies in several respects. These differences can account for the failure of others, and the success of the present inventors, in finding polymorphisms associated with BP. These difference include: (1) others reported **pedigree-**

based studies, while the present invention relates to a **population-based study**; (2) others did not use **linkage disequilibrium analysis**; and (3) others **included irrelevant phenotypes**, while the present study **excluded irrelevant phenotypes**. These differences were described in detail in the response to the January 20, 2000 Office Action. *Since the cited studies could not have provided the kind of information that the instant inventors were able to provide, none of the cited art supports a conclusion of non-enablement of the instant claims.*

Applicants have described in detail how to identify additional polymorphisms associated with BP.

As noted above, Applicants have described in great detail: (1) Identification of a small interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification; (2) Identification of polymorphisms, e.g., allele 154 at D18S59, which associate with BP; and (3) How additional polymorphisms within the narrow interval can be identified in other BP patients. Those skilled in the art can thus identify, using the guidance in the specification, a polymorphism(s) within the identified region that associate with BP. The specification provides both a narrow region that is associated with BP (namely, the region on chromosome 18 between SAVA5 and ga203) as well as polymorphisms within this region that associate with BP. Thus, the specification is indeed enabling for a method of detecting the presence of a BP susceptibility polymorphism in an individual.

Nevertheless, and solely in the interest of expediting prosecution, the following claim amendments are made. Claim 1 is amended to recite a method of detecting an increased susceptibility to develop BP, comprising analyzing a sample of DNA from a test individual for the presence of a DNA polymorphism in the identified region, wherein the presence in the test individual of a polymorphism which is present on a disease chromosome indicates that the test individual has an increased susceptibility to develop BP.

New claim 27 is directed to a method of detecting the presence of a bipolar mood disorder susceptibility polymorphism in an individual comprising analyzing a sample of DNA from said individual for the presence of a DNA polymorphism on the short arm of chromosome 18 between SAVA5 and ga203; and determining the frequency of the polymorphism on disease chromosomes and non-disease chromosome, wherein an overrepresentation of the polymorphism on the disease chromosome indicates that the DNA polymorphism is associated with a form of bipolar mood disorder. Support for new claim 27 is found throughout the specification, and in particular on page 24, lines 10-22, wherein analysis of unrelated individuals allowed identification of polymorphisms associated with BP; page 27, line 22 to page 29, line 29; and page 14, lines 4-13.

This ability to identify polymorphisms associated with BP by analyzing DNA samples of unrelated individuals was made possible by using the information gained from analysis of the isolated study population. These studies allowed the inventors to identify the narrow interval defined by SAVA5 and ga203 as an interval containing polymorphisms associated with BP. Thus, from the entire genome, the inventors identified a narrow region which associates with BP, and which was found to contain polymorphisms associated with BP. Because this narrow interval was identified, one skilled in the art can, as described in the specification, analyze a sample of DNA from said individual for the presence of a DNA polymorphism on the short arm of chromosome 18 between SAVA5 and ga203, and determine the frequency of the polymorphism on disease chromosomes and non-disease chromosomes, wherein an overrepresentation of the polymorphism on the disease chromosome indicates that the DNA polymorphism is associated with a form of bipolar mood disorder.

Applicants submit that the rejection of claims 1-12 and 17-24 under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above and further in view of the amendments to the claims discussed above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §112, first paragraph ("written description")

Claims 1-12 and 17-24 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office Action stated that the specification "only described a linkage analysis of known markers in phenotypically diagnosed bipolar in families," and that this linkage "does not support the genus of claimed methods for detecting bipolar mood disorder susceptibility polymorphisms because the disclosed studies do not teach a representative number of species of the genus of polymorphisms encompassed by the claims." Office Action, page 10. Applicants respectfully traverse.

The Office Action stated that a polymorphism "includes point mutations, small deletions, insertions within and around a bipolar disease locus none of which have been described in the specification." Applicants respectfully note that the allele sizes of the microsatellite markers which Applicants identified as associated with BP are polymorphisms. Applicants are not required, under 35 U.S.C. §112, first paragraph, to provide each and every possible polymorphism. Applicants have pointed out a sufficient number of polymorphisms, as shown in Table 1, page 24 of the instant specification, to inform those skilled in the art that Applicants were in possession of the invention as of the filing date.

Applicants submit that the rejection of claims 1-12 and 17-24 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw this rejection.

III. CONCLUSION

Applicants submit that all claims are now in condition for allowance, which action is respectfully requested. If the Examiner finds that a telephone conference would expedite prosecution, the Examiner is invited to telephone the undersigned at the number provided below.

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Atty Dkt. No.: 6510-142 CON
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This response is being filed with a Petition for an Extension of Time, a Fee Transmittal sheet with authorization to charge the fee of $110.00 to Deposit Account No. 50-0815, order number 6510-142CON. The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number 6510-142CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct. 30, 2000

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